Experts’ comments:
Metformin, a first-line antidiabetic drug belonging to the biguanide family, has been associated with a decreased risk of subsequent cancers and an improved cancer-related outcome [1]. In a meta-analysis of 20 studies including >13,000 cancer patients with type 2 diabetes, metformin use increased overall survival by 34% and cancer-specific survival by 38% for all patients with cancer compared with nonmetformin use [2].

In patients with PCa treated with external-beam radiation therapy, metformin use was associated with improvement in all outcomes compared with the diabetic nonmetformin group. In men experiencing biochemical failure, metformin use was also independently correlated with a decrease in the development of castration-resistant PCa (CRPC) [3]. In nondiabetic patients with chemotherapy-naive CRPC, metformin use led to disease stabilization and prolongation of prostate-specific antigen doubling time in some patients [4].

The antineoplastic activity of metformin has been related to reduced hyperinsulinemia and glycemic levels. In addition, metformin selectively blocks the growth of cancer stem cells and inhibits the metabolic stress response that may stimulate the inflammatory pathway associated with a number of cancers. Because metformin is not believed to influence the transformation of benign cells to malignant cells but rather to modulate cellular energy, metformin may have a greater impact on cancer survival than on incidence. Metformin may also have other benefits for nondiabetic patients who require androgen deprivation therapy (ADT) through its insulin-sensitizing effects because ADT can be associated with insulin resistance and metabolic syndrome.

Because metformin is inexpensive, with only minor side effects in men with and without diabetes, and because PCa is a slow-growing disease, this drug could play a role in secondary prevention strategies [5]. Further studies are necessary to show which PCa patients may benefit from this therapy.

Conflicts of interest: The author has nothing to disclose.

References
The concerning methodology in the study by Finkle et al. is the authors’ use of men taking PDE5-Is as a purported benign control group. PDE5-Is were originally developed as a treatment for cardiovascular diseases such as angina [3] and are currently approved by the US Food and Drug Administration as treatments for pulmonary hypertension. They also have known cardiovascular benefits [3] including findings from a recent randomized placebo-controlled trial that showed PDE5-I use in heart failure patients was associated with improvements in left ventricular ejection fraction, diastolic function, exercise tolerance, and overall clinical condition [4]. The potential cardiovascular benefits of PDE5-Is may have contributed to the differences in MI rates found in the study, and this limitation was not discussed in the publication. Neither Vigen et al. nor Finkle et al. evaluated serum testosterone levels after beginning TST. Consequently, it is difficult to ascertain whether these men were compliant with the medication or even responded to therapy.

Multiple previous studies have found that low testosterone is associated with an increased risk of cardiovascular disease [5] and that TST is associated with a reduction in mortality in hypogonadal men [6]. The increased rate of MIs in the TST cohort of the Finkle et al. study may have been the result of preexisting cardiovascular risk factors present within the low testosterone group that were not present in the PDE5-I group. As mentioned previously, it is also possible that PDE5-I use in the so-called control group provided some cardiovascular-protective effect.

The question now becomes how these results affect clinical practice. There is clearly a need for large prospective placebo-controlled randomized trials such as the Women’s Health Initiative to determine definitively the cardiovascular risks of TST. However, until this occurs, physicians should consider adding to their patient counseling a discussion about putative cardiovascular risks associated with TST including the limitations of the current studies. The recent publications described represent an opportunity for well-informed physicians to have thorough discussions with their patients about the risks and benefits of TST and, if prescribed, to enter into an agreement with the patient to enable appropriate oversight during treatment.

Conflicts of interest: Larry I. Lipshultz participates in clinical trials and is a consultant and speaker for both Auxilium and Endo. The other authors have nothing to disclose.

References


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Re: Global Effects of Smoking, of Quitting, and of Taxing Tobacco
Jha P, Peto R.

Experts’ summary:
In this outstanding review, Jha et al. [1] summarize the reasons and effects of smoking on global health, highlighting the benefits of smoking cessation and discussing reasons affecting tobacco consumption. Still approximately 50% and 10% of young men and women, respectively, take up smoking with relatively few ever stopping. This has led to a steady increase in the annual tobacco-attributable death toll. Interestingly, smoking patterns have changed over the last century. Initially, smoking rates increased substantially in many high-income countries, followed by increasing rates in the middle- and low-income countries. In addition increasing rates of daily cigarette consumption were observed during the last century with comparable changes according to the income classes.

The authors found that in middle age patients, mortality rates among cigarette smokers were 2–3 fold increased compared to never smokers. Throughout adulthood this likely leads to a reduction in life span by an average of about 10 years, which mainly impairs the life expectancy of those killed by smoking in the middle age, as those otherwise might have had a life expectancy of decades. In contrast, smoking cessation increases life expectancy. Tobacco taxes and consumption are clearly inversely related especially in low-income and less educated groups. Moreover, banning advertisement may further help decrease overall consumption. Although most former smokers quit unaided, physician support or multimedia based counseling can increase the likelihood of successful quitting. The authors estimated that decreasing smoking prevalence could prevent several tens of millions of tobacco-attributable deaths during the next few decades.

Experts’ comments:
Tobacco use is a major preventable cause of premature death and disease worldwide. Smoking is the best-established